doi: 10.1111/j.1744-313X.2006.00626.x

# Th-1 cytokines gene polymorphism in human brucellosis

**S. Davoudi,* A. A. Amirzargar,† M. Hajiabdolbaghi,* M. Rasoolinejad, A. Soodbakhsh,* S. Jafari,* H. Piri,‡ P. Maleknejad,‡ H. Bagherian,* N. Madadi† & B. Nikbin†**

## Summary

Brucellosis is a worldwide zoonosis. Infection with *Brucella* species results in the activation of cell-mediated immune response. The interaction between Th1and Th2 cytokines determines the outcome of disease. Production of each cytokine is in turn affected by genetic factors. In this study, we investigated the possible association between Th1 cytokines gene polymorphism and brucellosis. Different genotypes of TNF-α, IFN-γ and IL-2 were determined by polymerase chain reaction–sequence-specific primer in 47 patients with brucellosis and in 166 healthy controls. Allele frequencies of these genotypes were compared using the $\chi^2$ test. The results showed a significant difference in the TNF-α genotype GG/GG in patients in comparison with controls (76.7% vs. 21%) ($P$ = 0.001, OR = 12.42, 95%CI 5.7–27.7). There was no significant difference in the frequency distribution of the IFN-γ genotypes between two groups. IL-2 GG genotype at position –330 was about two times more common in cases than in controls, but the difference was not significant (10.6 vs. 4.6 $P$ value = 0.09).This study shows that genetically low producers of TNF-α are possibly susceptible to brucellosis and raise doubt about the role of gene polymorphism of INF-γ in brucellosis which was demonstrated in previous studies. It seems that patients with brucellosis did not have a defect in producing IL-2 with even a trend towards producing higher amounts of this cytokine.

## Introduction

Brucellosis has most likely been present in human populations ever since the domestication of animals. There are four *Brucella* species that cause disease in humans: *B. melitensis*, *B. suis*, *B. abortus* and *B. canis*, in descending order of pathogenicity. Transmission of the disease to humans occurs through the consumption of infected, unpasteurized milk products, direct contact with infected animal parts and inhalation of infected aerosolized particles. Brucellosis exists worldwide, especially in Africa, Asia, Middle East, and Central and South America. In Iran in 2003, 17 765 cases of brucellosis were reported (Lim & Rickman, 2004; Pappas *et al*., 2005).

Infection with *Brucella* species results in the activation of cell-mediated immune response. Patients with acute brucellosis display a Th1 type response with cell proliferation and production of interferon (IFN)-γ, interleukin (IL)-2 and IL-12, crucial lymphokines in the regulation and generation of the immune response (Rodriguez-Zapata *et al*., 1996; Giambartolomei *et al*., 2002). Tumour necrosis factor (TNF)-α production also seems to be necessary for full expression of macrophage antibrucella activity and immunopathology of disease (Caballero *et al*., 2000).

Apart from environmental factors and pathogen strain differences, host genetic factors are also major determinants of susceptibility to or outcome of infectious diseases (Hill, 1998). Overall expression and secretion of cytokines are dependent, at least in part, on genetic polymorphism within the promoter region or other regulatory sequences of cytokine genes. A polymorphism at site –330 in the promoter region of the IL-2 gene results in a (T→G) base change. Individuals who are homozygous for the G allele produce over three times the amount of IL-2 than their T/T and T/G counterparts. Similarly, individuals homozygous for polymorphic allele T at site UTR5644 of IFN-γ gene produce significantly higher amount of IFN-γ than those genotyped as TA or AA. Polymorphism at site –308 in the human TNF-α promoter region results in an A to G transition and a subsequent 6- to 7-fold increase in transcriptional activity (Hoffman *et al*., 2001). In this study we investigated the possible association between genotypes of three Th1 cytokines and brucellosis.

## Materials and method

During a 2-year period (2002–04) all patients with brucellosis attended an infectious diseases ward of a teaching hospital in Tehran University of Medical Sciences, Iran, were enrolled in the study. Brucellosis was diagnosed according to compatible epidemiological and clinical findings together with serological and/or bacteriological

* Department of Infectious Diseases, Imam Hospital, Tehran University of Medical Sciences, † Department of Immunogenetics, Faculty of Medicine, Tehran University of Medical Sciences and ‡ Department of Microbiology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Received 13 June 2006; 1st revision 9 May 2006; 2nd revision 13 June 2006; accepted 20 July 2006

Correspondence: Alia kbar Amirzargar, Immunogenetic Laboratory, Department of Immunology, Medical school, Tehran University of Medical Sciences, Tehran, Iran. Tel: +9821-88953009; Fax: +9821-66422337; E-mail: Amirzargar_ali@yahoo.com

 